PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 :
C07H 19/10, 19/20; C07F 9/65
A61K 31/70, 31/675

A1

(11) International Publication Number: WO 84/ 04748

(43) International Publication Date: 6 December 1984 (06.12.84)

(21) International Application Number: PCT/US84/00737

(22) International Filing Date: 14 May 1984 (14.05.84)

(31) Priority Application Number: 497,720

(32) Priority Date: 24 May 1983 (24.05.83)

(33) Priority Country: US

(71) Applicant: SRI INTERNATIONAL [US/US]: 333 Ravenswood Avenue, Menlo Park, CA 94025 (US).

(72) Inventors: REIST, Elmer, Joseph ; 581 Berkeley Avenue, Menlo Park, CA 94025 (US). STURM, Priscilla, Anna ; 1549 Montalvo Drive, Mountain View, CA 94040 (US).

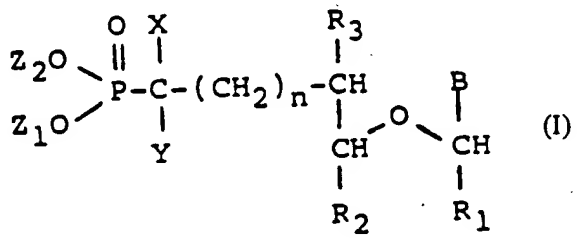
(74) Agent: FAUBION, Urban, H.; SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025 (US).

(81) Designated States: DE, FR (European patent), GB, JP, NL, SE.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

FOR YOUR PATENT NEEDS
AML Information Services
P.O. Box 405
Corte Madera, CA 94925
415-927-0340

(54) Title: NOVEL ANTIVIRAL AGENTS



(I)

(57) Abstract

Phosphonate analogues of mono-, di-, and triphosphates of antiviral nucleoside analogues. These materials are represented structurally as formula (I), wherein Z_1 and Z_2 are the same or different and selected from the group made up of hydrogen, the one to six carbon alkyls, phenyl and benzyl, X is H, OH, or together with Y = O, Y is H or together with X = O, n is an integer, 0, 2 or 4, R_1 and R_2 together complete a β-pentofuranose sugar or R_1 is H and R_2 is H or $-CH_2OH$. R_3 is H or OH and B is a pirine or pyrimidine base. These materials have antiviral activity, expecially against herpes virus. Antiviral pharmaceutical preparations and their use are disclosed as well.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	KR	Republic of Corea
AU	Australia	LI	Liechtenstein
BE	Belgium	LK	Sri Lanka
BG	Bulgaria	LU	Luxembourg
BR	Brazil	MC	Monaco
CF	Central African Republic	MG	Madagascar
CG	Congo	MR	Mauritania
CH	Switzerland	MW	Malawi
CM	Cameroon	NL	Netherlands
DE	Germany, Federal Republic of	NO	Norway
DK	Denmark	RO	Romania
FI	Finland	SD	Sudan
FR	France	SE	Sweden
GA	Gabon	SN	Senegal
GB	United Kingdom	SU	Soviet Union
HU	Hungary	TD	Chad
JP	Japan	TG	Togo
KP	Democratic People's Republic of Korea	US	United States of America

NOVEL ANTIVIRAL AGENTS

Field of the Invention

This invention concerns nucleotide analogues and their synthesis and use. More particularly, it concerns phosphonic acid analogues of natural and synthetic nucleoside phosphates and their preparation and use as antiviral agents.

Background of the Invention

There is a recognized need for antiviral agents. Herpes virus hominis alone infects between 50 and 150 million Americans at this time. A number of the antiviral agents that are currently viewed as most effective against herpes are nucleoside analogues. These materials include iododeoxyuridine, 2-hydroxyethoxymethylguanine, 2'-fluoro-5-iodo-1-arabinofuranosyl cytosine and 5-E-bromovinyldeoxyuridine. It is believed that these materials act through their conversion by viral thymidine kinase (but not by host TK) to the nucleotide which is then converted to the triphosphate and incorporated into viral DNA. The incorporation of these analogues into the viral DNA prevents its replication and thus is lethal to the virus. Two shortcomings of this antiviral mechanism have been recognized, however. First, thymidine kinase negative herpes mutants (TK^-) have been identified which are inherently inactive toward phosphorylating these analogues and thus permitting their incorporation in viral DNA. In addition, TK^+ mutants that are resistant to 2-hydroxyethoxymethylguanine have been reported in mice by H. Field, et al, in J Infect Dis, 143 281 (1981). TK^+ mutants resistant to iododeoxyuridine have been reported in

BUREAU OMPI WIPO INTERNATIONAL

humans by A. Hirano, et al, in Acta Virol 23 226 (1979). It may be that these newly-discovered resistant viral strains do not undergo the monophosphorylation or triphosphate formation needed to permit incorporation in the DNA.

References to these antiviral agents of the art and their use include Am J Med, 73 No 1A, July 20, 1982 "Proceedings of a Symposium on Acyclovir"; Biochem Biophys Acta, 32 295-6 (1959); Antimicrob Agents Chemother, 578-584 (1965); Science, 145 585-6 (1964); Science, 255 468-80 (1975); J Med Chem, 19 495-8 (1976); Proc Natl Acad Sci, 76 4415-18 (1979); and J Med Chem 22 21-24 (1979).

The present invention provides antiviral materials which can be lethally incorporated into DNA without the dependence upon enzyme-moderated phosphorylation. The materials of the invention are phosphonate analogues of the mono-, di- and triphosphates of the deoxynucleotide analogs. An article by Robert Engel appearing at Chem Reviews, 11, #3 pp 349-367 (1977) discusses phosphonate analoges of nucleotides and the like. Other representative references in this area, some of which are cited in the Chem Reviews article, are German O.L.S 2,350,608 (1974) of Syntex (Jones and Moffatt inventors); German O.L.S. 2,009,834 1970 also of Syntex with Jones and Moffatt as inventors; British Patent 1,243,214 of Syntex, and US Patent 3,560,478 of Myers.

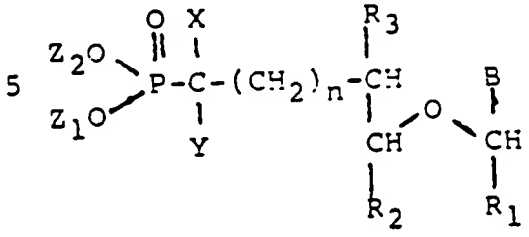
request these patents. *

Statement of the Invention

A group of new materials have now been found. These materials in a broad sense are phosphonate analogues of mono-, di-, and triphosphates of antiviral nucleoside analogues. These analogues

BUREAU OMPI WIPO INTERNATIONAL

differ from nonlethal natural nucleosides by variations in their sugar ribose moiety and/or by variations in their nucleoside base moieties. Such materials are represented structurally as



wherein Z_1 and Z_2 are the same or different and selected from the group made up of hydrogen, the one to six carbon alkyls, phenyl and benzyl, X is H, OH, or together with Y = O, Y is H or together with X = O, n is an integer, 0, 2 or 4, R_1 and R_2 together complete a β-pentofuranose sugar or R_1 is H and R_2 is H or $-CH_2OH$, R_3 is H or OH and B is a purine or pyrimidine base.

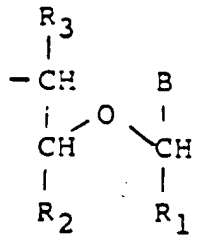
In other aspects this invention relates to the preparation of these materials, their formulation into antiviral pharmaceutical compositions and the use of these formulations to treat viral infections, in particular herpes infections.

Detailed Description of the Invention

The compounds

The compounds of this invention are phosphonates which have the structure set forth above in Statement of the Invention.

BUREAU OMPI WIPO INTERNATIONAL



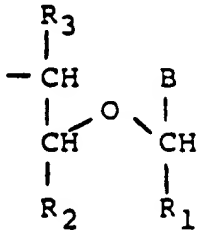
The unit defines an antiviral nucleoside.

As previously noted, in this structure R_1 and R_2 can together complete a β-pentofuranose sugar. In this configuration they preferably complete a substituted or unsubstituted β-ribofuranose or β-arabinofuranose such as ribose, 2-deoxyribose, 2,3-dideoxyribose, 3-deoxyribose, 2-fluoro-2-deoxyribose or arabinose or the like.

In this structure, Z_1 and Z_2 preferably are each selected from hydrogens and one to four carbon alkyls. More preferably Z_1 and Z_2 are each hydrogens. Further in this structure, the integer n is significant in defining whether the compound is in size equivalent to a nucleoside monophosphate, a diphosphate or a triphosphate.

Preferred bases include guanine, adenine, 5-iodouracil, 5-trifluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil, 5-propyluracil, and 5-ethyluracil.

Preferred nucleoside analogues (e.g.

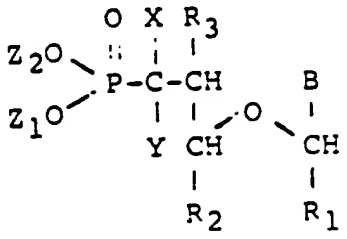


include 5-iodo-2'-deoxyuridine, 9-B-D-arabinofuranosyladenine, 5-trifluorothymidine, E-5-(2-bromovinyl)-2'-deoxyuridine, 1-(2'-deoxy-2'-fluoro-B-D-arabino-

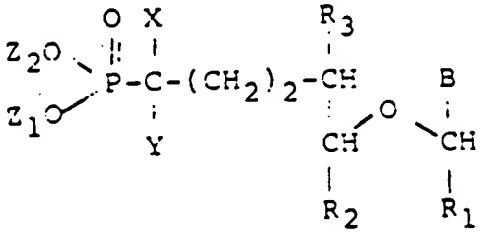
BUREAU OMPI WIPO INTERNATIONAL

furanosyl)-5-iodocytosine, 5-ethyl-2'-deoxyuridine, 5-propyl-2'-deoxyuridine, 9-(2-hydroxy-ethoxymethyl)guanine, 9-(ethoxymethyl)guanine, 9-(2-hydroxy-ethoxymethyl)adenine and 9-(ethoxymethyl)adenine.

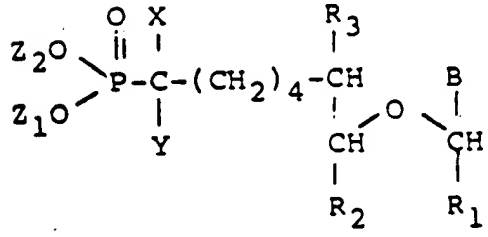
These nucleoside analogues yield phosphonates (and di- and triphosphate-phosphonate analogues) having the following general structures



,



and

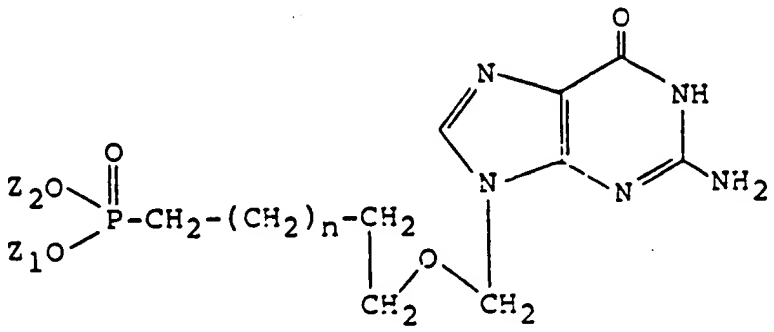
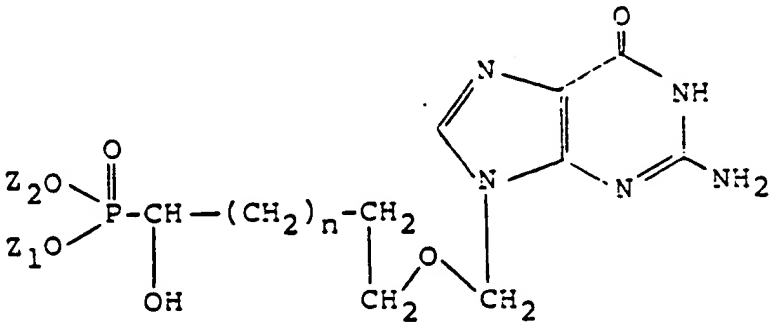
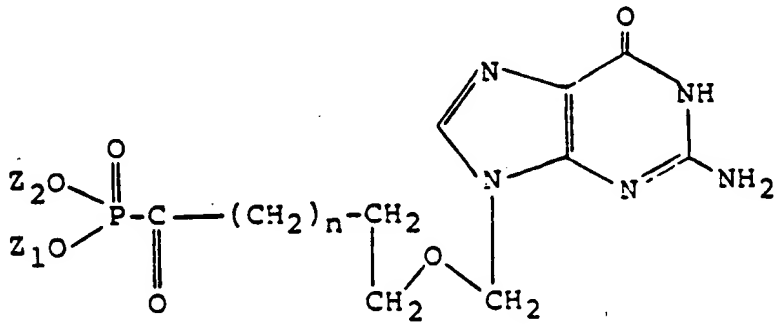


wherein X, Y, Z_1, Z_2, B, R_1, R_2 and R_3 are as described above. In preferred embodiments, X is hydrogen or hydroxyl and Y is hydrogen. Thus, representative compounds can have the structures shown in Table I.

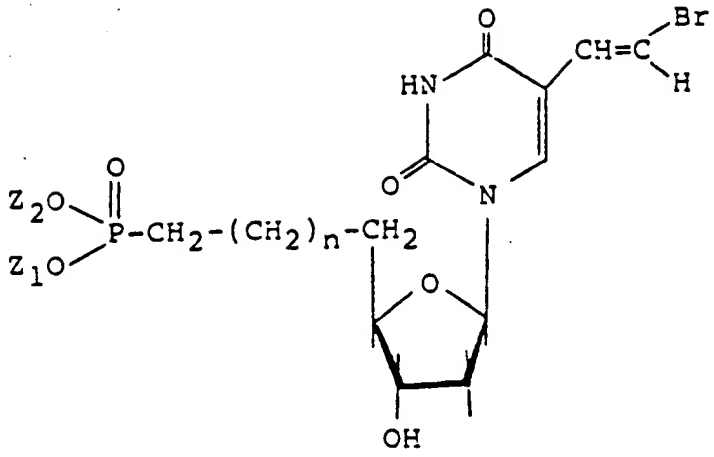
BUREAU OMPI WIPO INTERNATIONAL

Table I

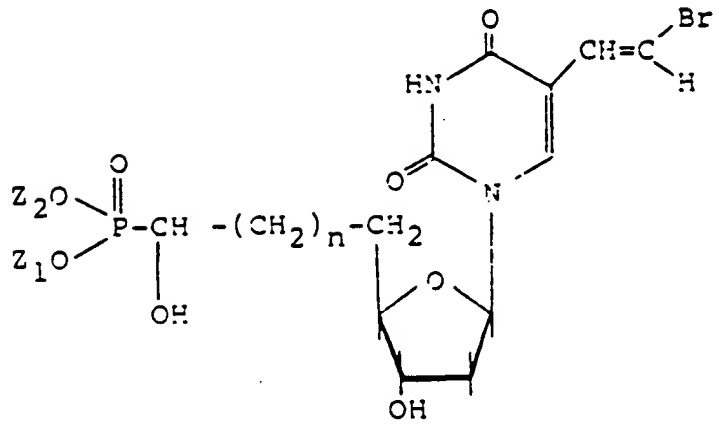
Representative Structures

Structure	Structure Number
	1
	2
	3

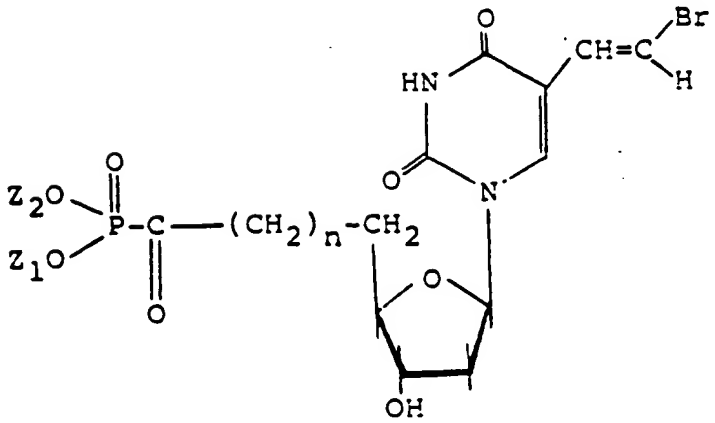
BUREAU OMPI WIPO INTERNATIONAL



4

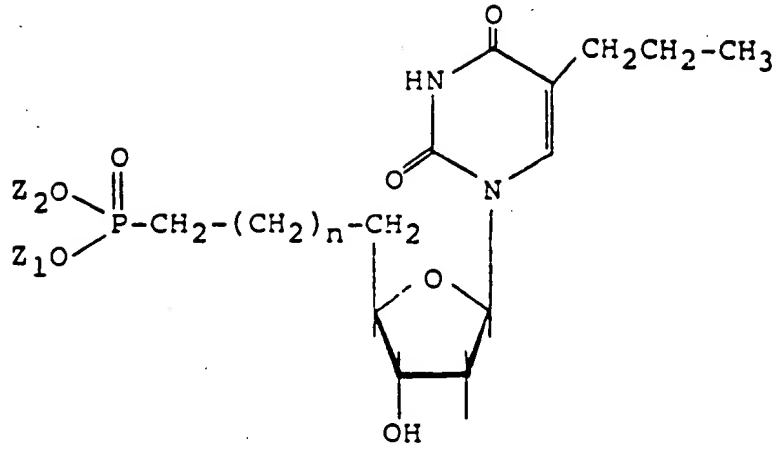


5

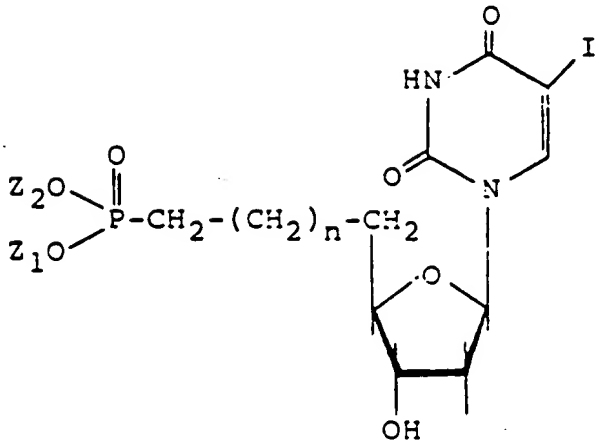


6

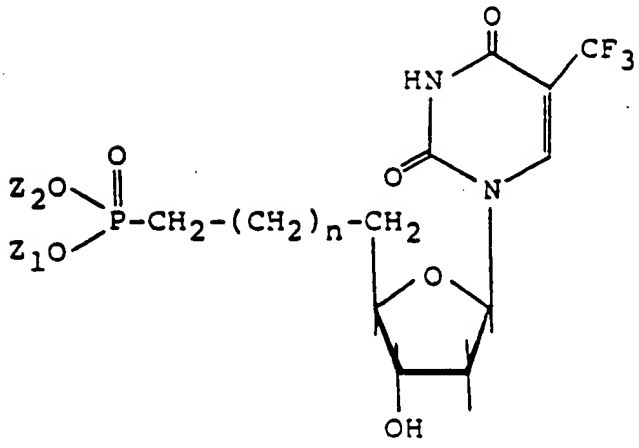
BUREAU OMPI WIPO INTERNATIONAL



7

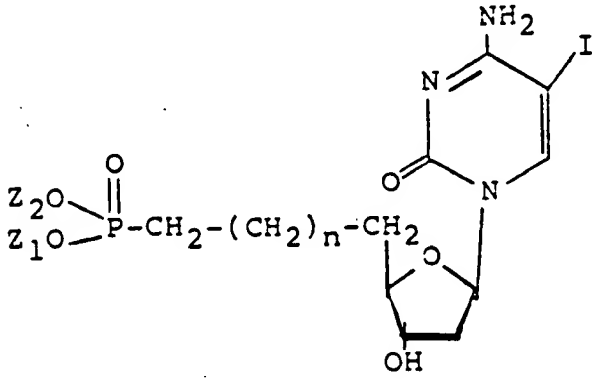


8

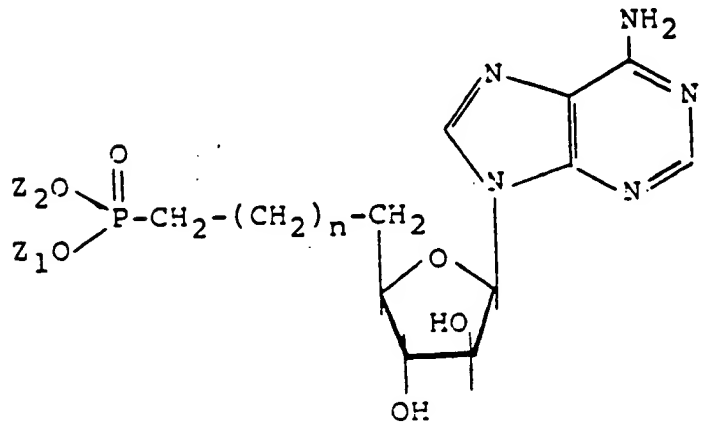


9

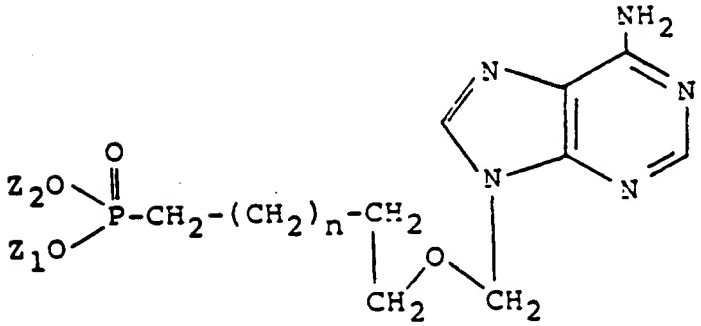
BUREAU OMPI INT. WIPO



10

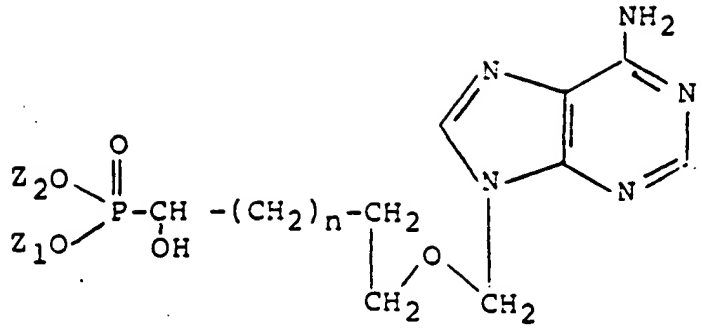


11

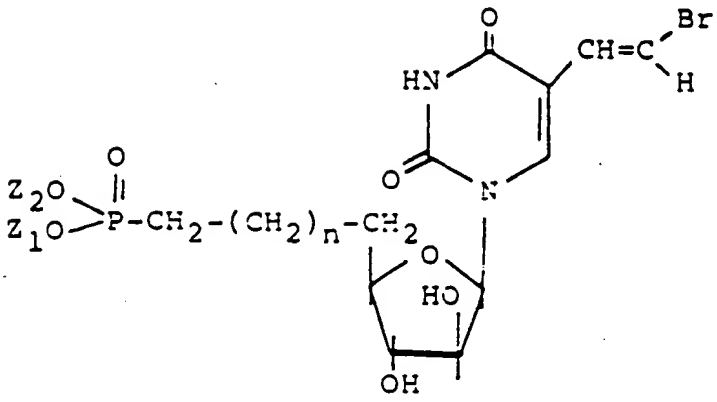


12

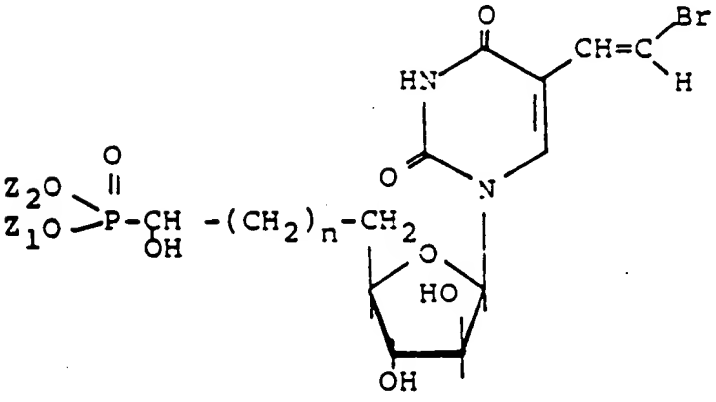
BUREAU OMPI WIPO INTERNATION



13

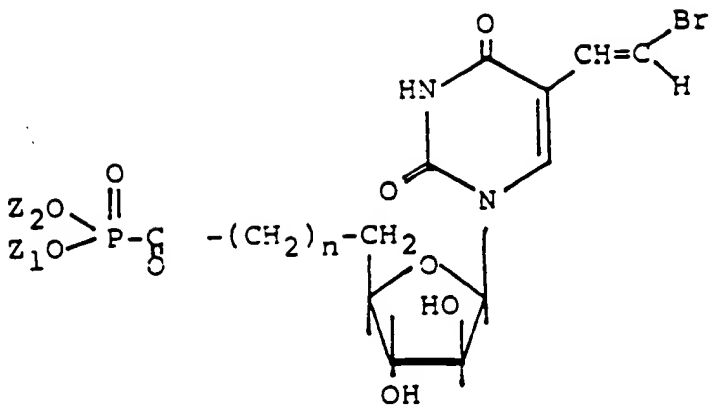


14

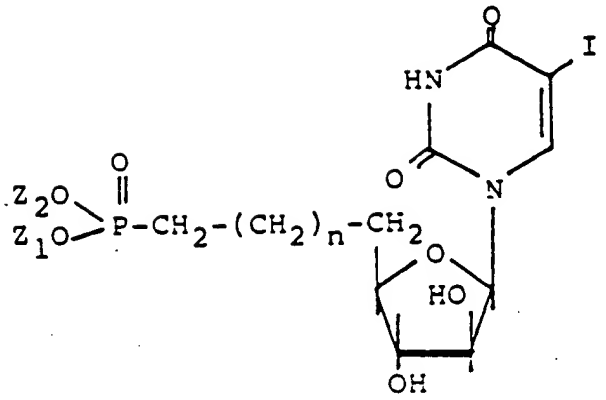


15

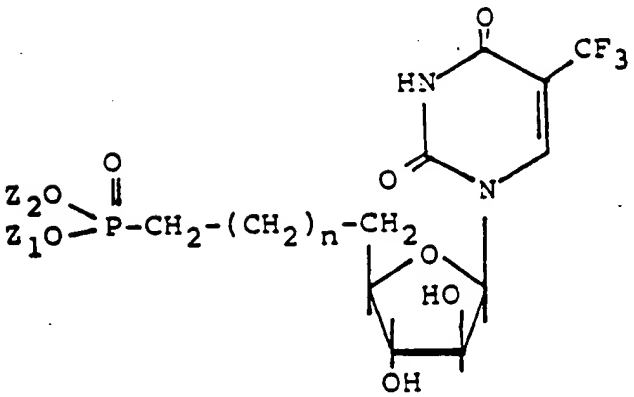
BUREAU OMPI WIPO



16

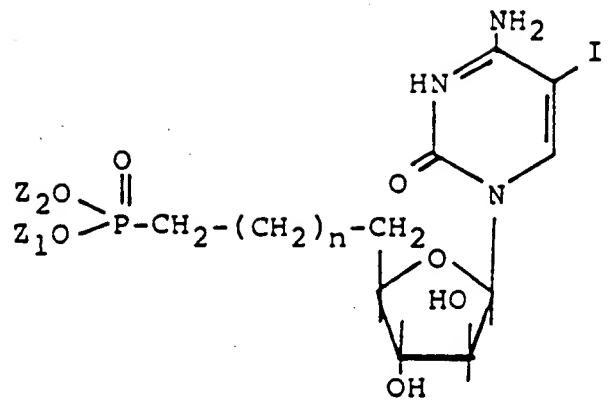


17

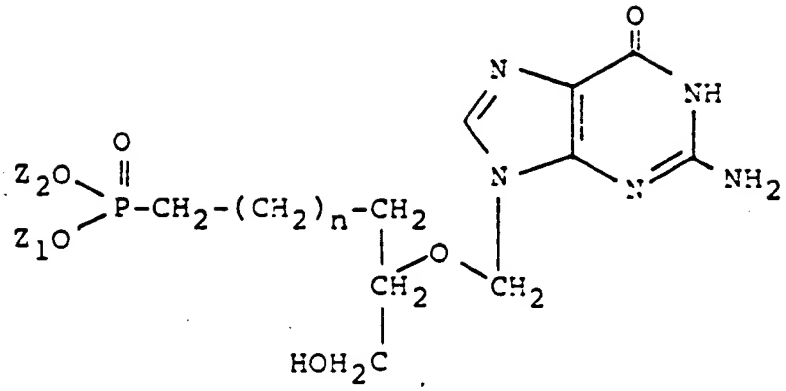


18

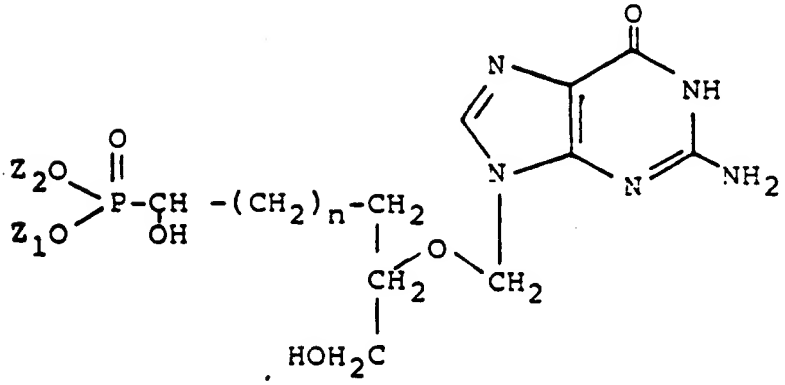
BUREAU OMPI WIPO



19

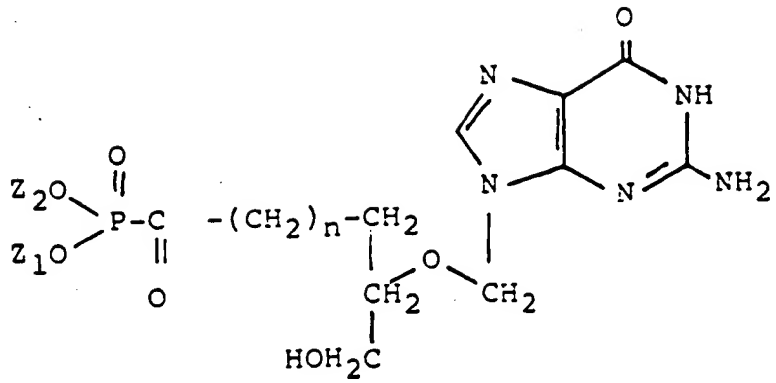


20



21

BUREAU OMPI WIPO



22

Table II

Representative Compounds

Monophosphate Analogues

Compound Number	Structure Number	Z_1	Z_2	n
1a	1	H	H	O
1b	1	CH_3	CH_3	O
1c	1	H	CH_3	O
1d	1	H	C_2H_5	O
2a	2	H	H	O
2b	2	CH_3	CH_3	O
2c	2	H	CH_3	O
2d	2	H	C_2H_5	O
3a	3	H	H	O
3b	3	CH_3	CH_3	O
3c	3	H	CH_3	O
3d	3	H	C_2H_5	O
⋮				
22a	22	H	H	O
22b	22	CH_3	CH_3	O
22c	22	H	CH_3	O
22d	22	H	C_2H_5	O

BUREAU OMPI WIPO

Diphosphate Analogs

Compound Number	Structure Number	Z_1	Z_2	n
1e	1	H	H	2
1f	1	CH_3	CH_3	2
1g	1	H	CH_3	2
1h	1	H	C_2H_5	2
2e	2	H	H	2
2f	2	CH_3	CH_3	2
2g	2	H	CH_3	2
2h	2	H	C_2H_5	2
⋮				
22a	22	H	H	2
22b	22	CH_3	CH_3	2
22c	22	H	CH_3	2
22d	22	H	C_2H_5	2

Triphosphate Analogues

Compound Number	Structure Number	Z_1	Z_2	n
1	1	H	H	4
1	1	CH_3	CH_3	4
1	1	H	CH_3	4
1	1	H	CH_3	4
⋮				
22	22	H	H	4
22	22	CH_3	CH_3	4
22	22	H	CH_3	4
22	22	H	C_2H_5	4

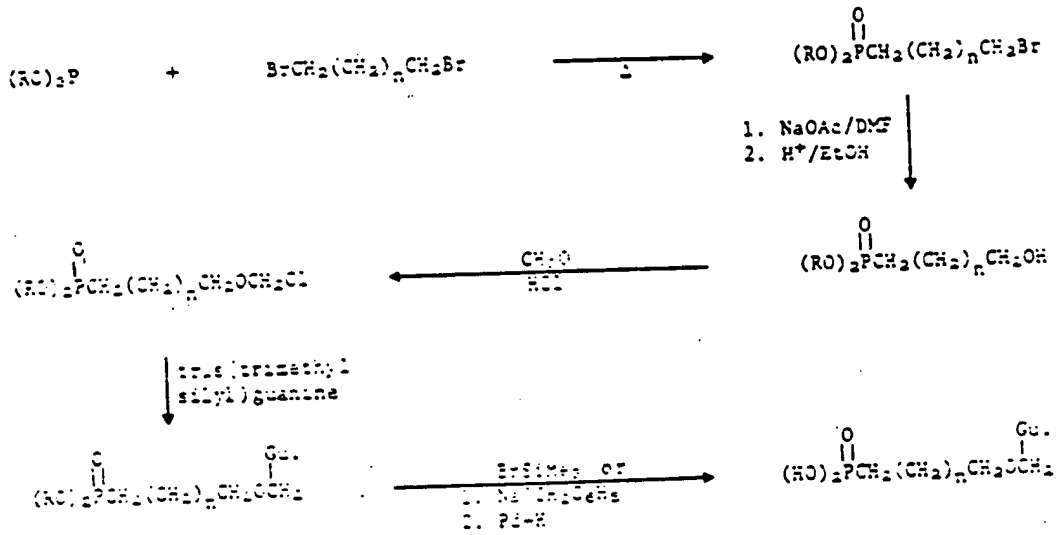
These are merely representative compounds as it will be apparent to those skilled in the art that other combinations of substituents and bases could be employed as well.

BUREAU OMPI WIPO INTERNATIONAL

Preparation

The compounds of this invention can be prepared by the following general procedures: The non β-pentofuranose materials such as materials having structures 1, 2, 12, 13, 20, 21, and 22 in Table I can be made with the representative reaction sequence I.

I.



Scheme I

In this sequence, a trialkyl (C_2, C_4 or C_6) phosphite reacts with a dibromoalkane in an Arbuzov reaction to give the bromoalkyl phosphonate (See J Am Chem Soc, 87 (2), 253 (1965)). (All cited references are incorporated herein).

Displacement of the bromide using sodium acetate in DMF followed by hydrolysis of the acetate ester gives diethyl 3-hydroxypropylphosphonate (i.e. in sequence I, R = C_2H_5, n = 1). This material is chloromethylated to the chloromethylester and then reacted with a suitably protected base such as tris-trimethylsilylguanine by the method of Kelley, et al.

BUREAU OMPI WIPO INTERNATIONAL

J Med Chem, 24 1523 (1981). This yields the phosphono product, e.g. 9-(3-phosphonopropyloxymethyl)guanine, directly. Phosphonate esters are smoothly cleaved by bromotrimethylsilane to the phosphonic ester by the method of McKenna, et al, Tet Letts, 155 (1977).

The syntheses of a representative deoxyriboside is illustrated in Scheme II.

Oxidation of 2',3'-O-isopropylidine-5-propyluridine (1) by the Moffatt procedure, Pfitzner and Moffatt J Am Chem Soc, 85 3027 (1963) will yield the 5'-aldehyde. The reaction of (2) by the Wittig reagent prepared as shown in Scheme (2) gives the chain-extended, unsaturated "nucleotide" (4). Hydrogenation and deacetonation of the nucleotide (4) will give the partially unblocked nucleotide (5).

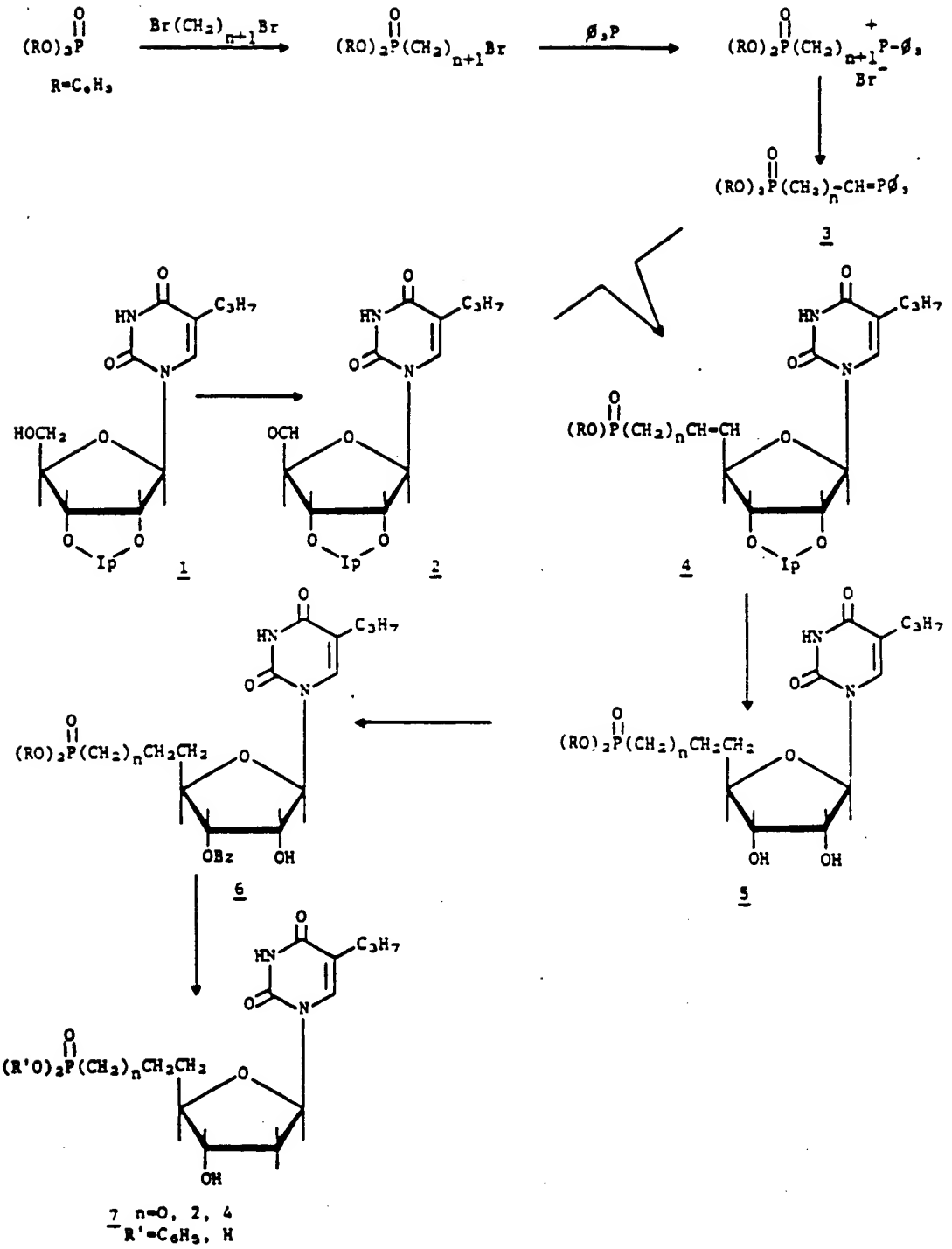
The conversion of the riboside (5) to the deoxyriboside (7) is accomplished by a strategy described recently by Lessor and Leonard, J Org Chem, 46 4300 (1981), which was based on the selective partial deacylation of fully acylated nucleosides outlined by Ishido, et al, J Chem Soc, Perk I, 563 (1980). Thus benzoylation of (5) to the 2',3'-di-O-benzoate followed by treatment with hydroxylaminium acetate in dry pyridine will give the 3'-benzoate (6). Thiobenzoylation of (6) followed by treatment with tributyl tin and debenzoylation using sodium benzyloxide, converts the 2'-hydroxyl to H, deacylates the 3'-O-benzoate, and substitutes the phenyl phosphate ester with benzyl phosphate, Jones and Moffatt J Am Chem Soc, 90 5337 (1968). Hydrogenolysis removes the benzyl ester and gives the desired phosphonic acid (7).

BUREAU OMPI WIPO INTERNATIONAL

Alternatively, compounds in the 2-deoxyribose series are prepared from the 2'-deoxynucleoside by chemistry outlined in Scheme III. Thus, selective tritylation followed by mesylation of 5-propyl-2'-deoxyuridine (1) gives (8), which is converted to the 2,3'-cyclonucleoside (9) using sodium benzoate in DMF (Yung and Fox, J Am Chem Soc, 83 3060 (1961)). Oxidation to the aldehyde (10) followed by a Wittig condensation gives the unsaturated phosphonate (11). Hydrogenation and ring-opening (Yung and Fox) gives the phosphonate ester (7), which can be deblocked, (U.S. Patent 3,524,846 and J Am Chem Soc, 90 5337 (1968)) to the free phosphonic acid. Hydroboration of (11) followed by ring mixture of 5'-hydroxy and 6'-hydroxy isomers.

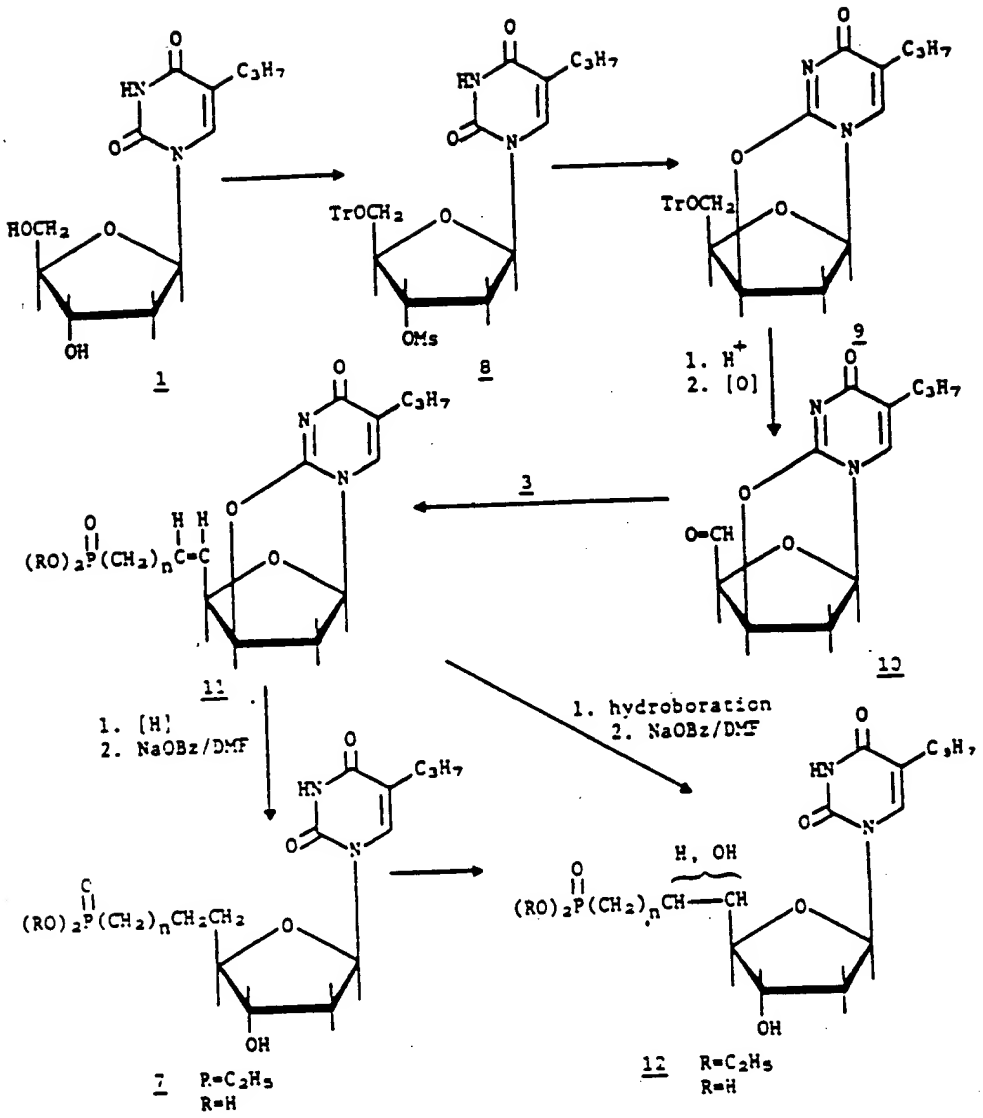
Oxygen functionality α to the phosphonate can be introduced by the chemistry outlined in Scheme IV. The appropriate propargyl phosphonic acid (13) can be prepared from tetrahydropyranyl-propargyl alcohol (12) by the procedures outlined by Chattha and Aquiar, J Org Chem. 36 2719-20 (1971). Selective hydrogenation to the vinyl phosphonate followed by the sequence outlined in Scheme IV results in phosphonate analogues with one or two hydroxyls in the phosphonate chain.

BUREAU OMPI WIPO INTERNATIONAL



Scheme II

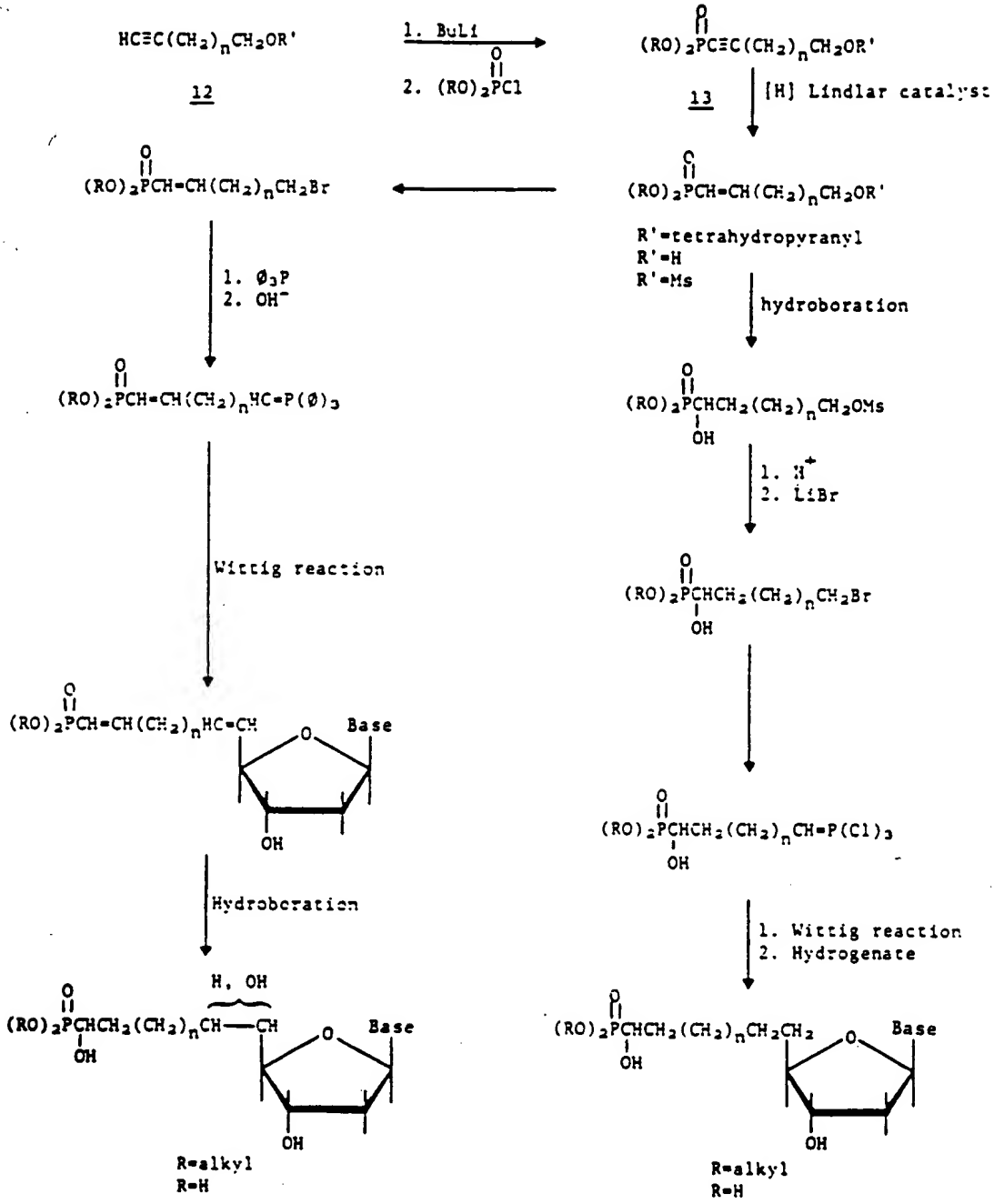
BUREAU OMPI WIPO INTERNATIONAL



Scheme III

does not say how make the primer

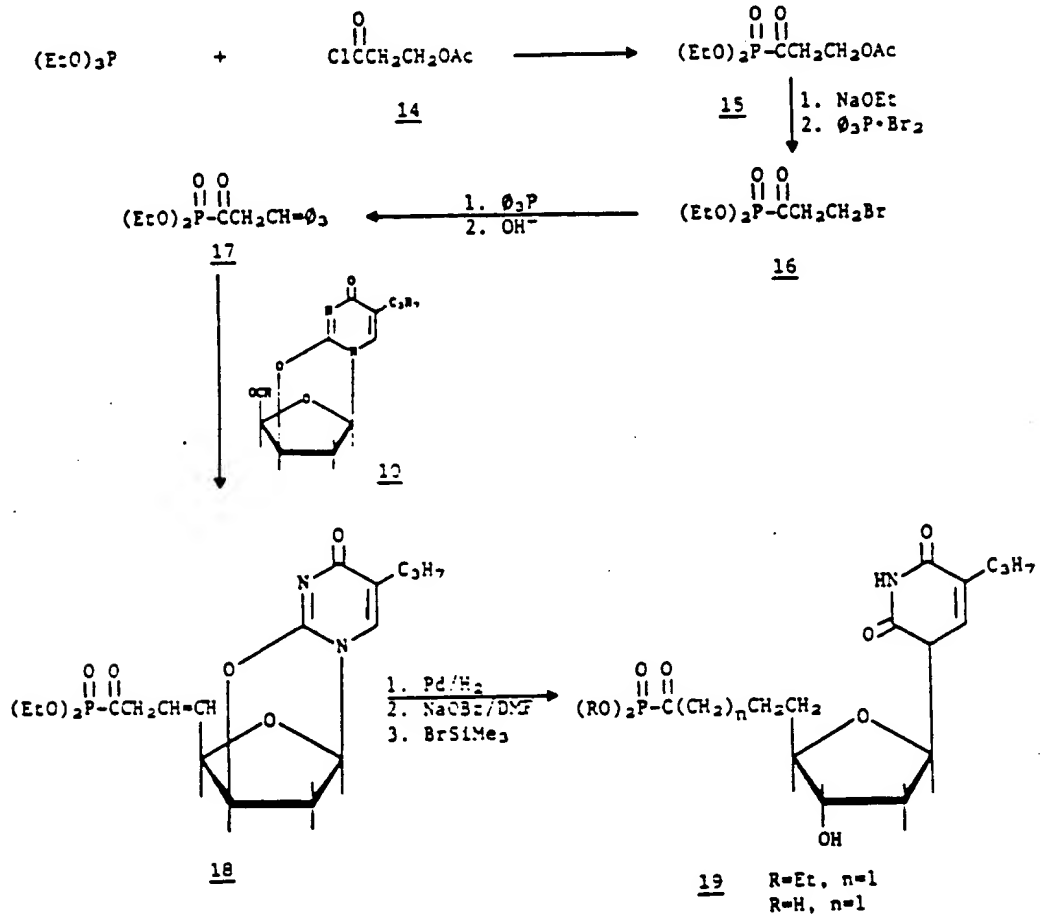
BUREAU OMPI WIPO INTERNATIONAL



Scheme IV

BUREAU OMPI WIPO INT...

Carbonyl analogs can be prepared by the chemistry outlined in Scheme V. This method involves Arbuzov reaction of triethylphosphite with β-acetoxy-propionyl chloride (14) by the method of Yamashita, et al, Bull Chem Soc Japan, 53(6) 1625 (1980).



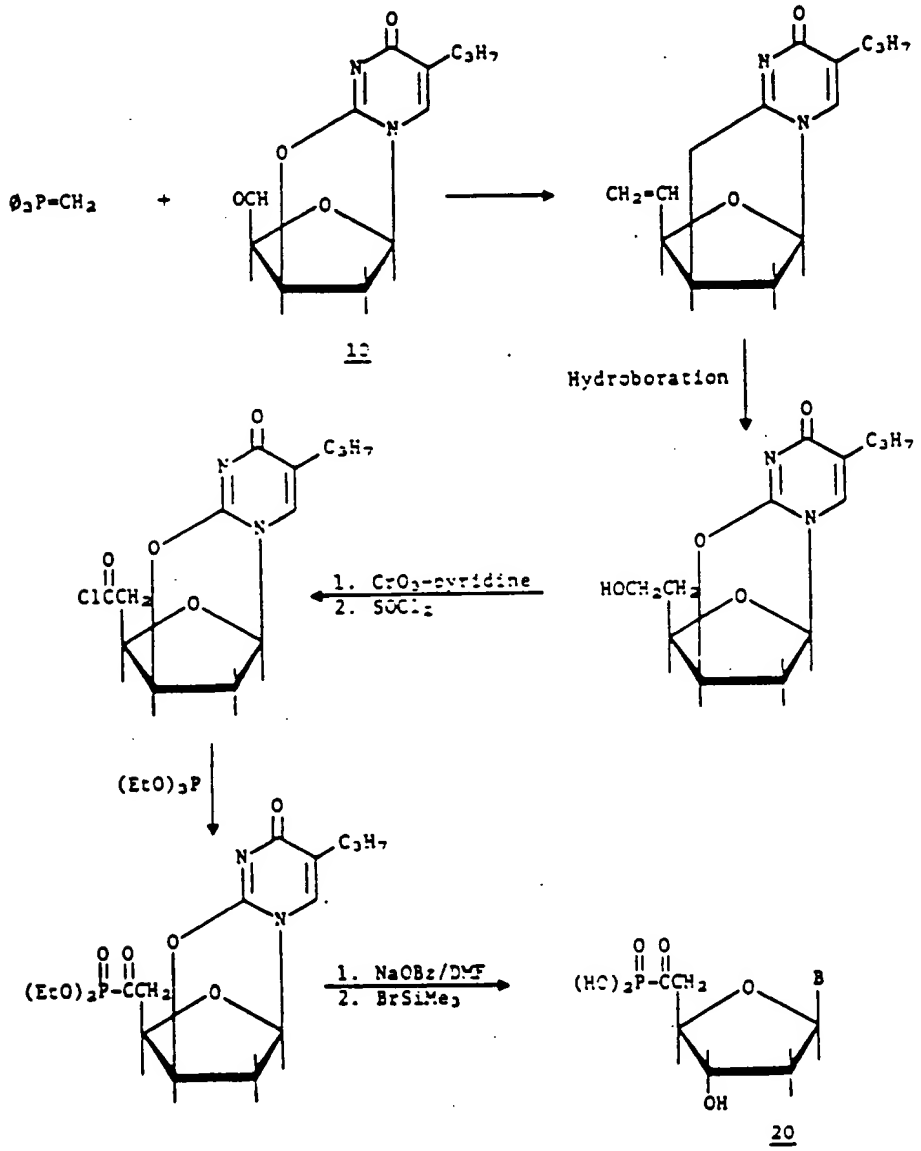
Scheme V

This gives the α-carbonyl phosphonate ester (15). Conversion of 15 to the bromoethyl derivative 16 followed by reaction with triphenylphosphine will give the Wittig reagent (17). Condensation of 17 with the appropriate aldehyde (e.g. 10) gives the olefin 18, which, after hydrogenation and deblocking, results in

BUREAU OMPI WIPO INT

the desired product 19, a nucleoside diphosphonate analog. The nucleoside triphosphate analog 19 (wherein n = 3) can be prepared starting from 5-acetoxyvalerylchloride.

The nucleoside monophosphonate analog (20) can be prepared by the chemistry outlined in Scheme VI.



19 20

Scheme VI

BUREAU OMPI WIPO INTERNATIONAL

Salts

Physiologically acceptable salts of compounds of this invention are prepared by methods known in the art. The salts include ammonium salts and salts of physiologically acceptable metals, particularly Li^+, K^+, Na^+, Ca^{++} and Mg^{++}, and are novel compounds and comprise a further aspect of the invention. Metal salts can be prepared by reacting a metal hydroxide with a compound of the invention. Examples of metal salts which can be prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from a solution of a more soluble salt by addition of a suitable metal compound. Acid salts can be prepared by reacting a compound of the invention with an acid such as HCl, HBr, H_2SO_4, or an organic sulphonic acid.

Pharmaceutical Preparations

The compounds of this invention (including the physiologically acceptable salts thereof) have antiviral activity. They present activity against Herpes Simplex viruses and related viruses for example Herpes Simplex virus I, Herpes Simplex virus II, Epstein-Barr virus, varicella Zoster virus, and cytomegalo virus. Thus the compounds can be formulated into pharmaceutical preparations. Such preparations are composed of one or more of the compounds in association with a pharmaceutically acceptable carrier. The book Remington's Pharmaceutical Sciences, 15th Ed by E.W. Martin (Mark Publ. Co., 1975) discloses typical carriers and methods of preparation, which disclosure is incorporated by reference.

The compounds may be administered topically, orally, parenterally (e.g. intravenously, by

BUREAU OMPI WIPO INTERNATIONAL

intramuscular injection, or by intraperitoneal injection or the like depending upon the nature of the viral infection being treated.

For internal infections the compositions are administered orally or parenterally at dose levels of about 0.1 to 300 mg/kg, preferably 1.0 to 30 mg/kg of mammal body weight and can be used in man in a unit dosage form administered one to four times daily in the amount of 1 to 250 mg per unit dose. For oral administration, fine powders or granules may contain diluting, dispersing and/or surface active agents, and may be presented in water or in a syrup, in capsules or sachets in the dry state or in a nonaqueous solution or suspension, wherein suspending agents may be included; in tablets, wherein binders and lubricants may be included, or in a suspension in water or a syrup. Where desirable or necessary, flavoring, preserving, suspending, thickening or emulsifying agents may be included. Tablets and granules are preferred oral administration forms and these may be coated.

For parenteral administration or for administration as drops, as for eye infections, the compounds may be presented in aqueous solution in a concentration of from about 0.1 to 10%, more preferably about 0.1 to 7%. The solution may contain antioxidants, buffers, etc.

Alternatively, for infections of the eye, or other external tissues, e.g. mouth and skin the compositions are preferably applied to the infected part of the body of the patient topically as an ointment, cream, aerosol or powder, preferably as an ointment or cream. The compounds may be presented in an ointment, for instance with a water soluble ointment base, or in a cream, for instance with an oil in water

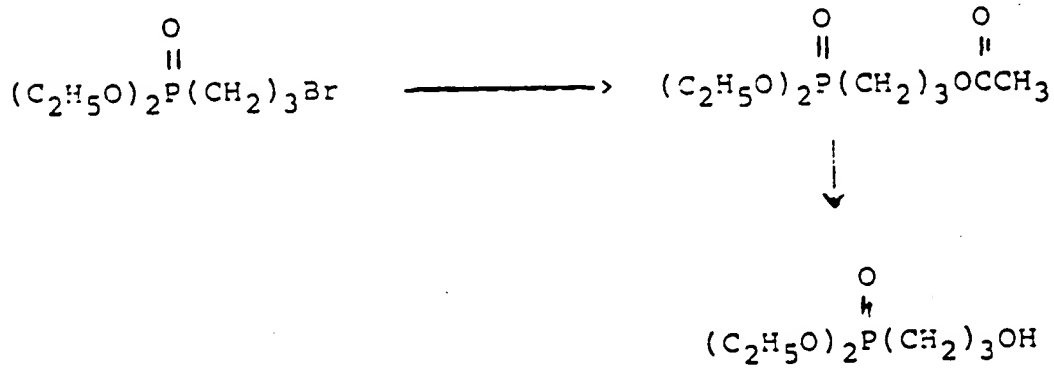
BUREAU OMPI WIPO INTERNATIONAL

cream base in a concentration of from about 0.01 to 10%, preferably 0.1 to 7%, most preferably about 0.5% w/v. Additionally, viral infections of the eye, such as Herpetic keratitus may be treated by use of a sustained release drug delivery system as is described in the art.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgement of the attending practitioner.

The invention will be further described by the following nonlimiting examples.

Example I



Diethyl-3-hydroxypropylphosphonate

Diethyl-3-bromophosphonate (12.0 g, 46 mmol, prepared by the method of Anatol Eberhard and F.H. Westheimer, JACS 87 253-260 (1965)) was stirred with 12.0 g $NaOAc \cdot 3H_2O$ in 125 ml DMF heated in a steam bath. The reaction was evaporated to dryness in vacuo after 2 hours and partitioned between H_2O and EtOAc, extracting the aqueous layer five times. The ethyl acetate extract was washed once with brine, dried with

BUREA OMPI WIPO INTER

Na_2SO_4. filtered, and evaporated to dryness in vacuo to yield 9.8 g light yellow oil (89%). ^1H NMR ($CDCl_3$) δ 1.3 (tr, 6 H), 1.5-2.0 (m, 4 H), 2.03 (s, 3 H), 4.1 (assym. quintet, 6 H)· thin layer chromatography on SiGF developed with 2:1 EtOAc:CH_2Cl_2 gave R_f 0.30. The isolated diethyl-3-acetoxypropylphosphonate (9.8 g, 41 mmol) in 200 ml abs. EtOH was stirred with 30 ml Dowex 50 (H^+) which had been rinsed three times each with H_2O and EtOH. After 4-1/2 days at room temperature, another 10 ml of similarly prepared resin was added. Six hours later, the reaction was filtered and evaporated in vacuo. The quantitative yield of yellow oil was purified by dry column chromatography on 400 g silica packed in a 2.75 inch flat diameter nylon tube. The column was eluted with 1:9 MeOH:EtOAc and the appropriate fractions were cut and slurried with 1:1 MeOH:EtOAc. Filtration and evaporation in vacuo afforded 5.33 g (66%) pale yellow oil. ^1H NMR ($CDCl_3$ D_2O): δ 1.30 (tr, 6 H), 1.60-2.08 (m, 4 H), 3.67 (tr, 2 H), 4.13 (quintet, 4 H); thin layer chromatography on SiGF developed with 1:9 MeOH:EtOAc gave an R_f of 0.57.

9(3-phosphono-1-propyloxymethyl)guanine

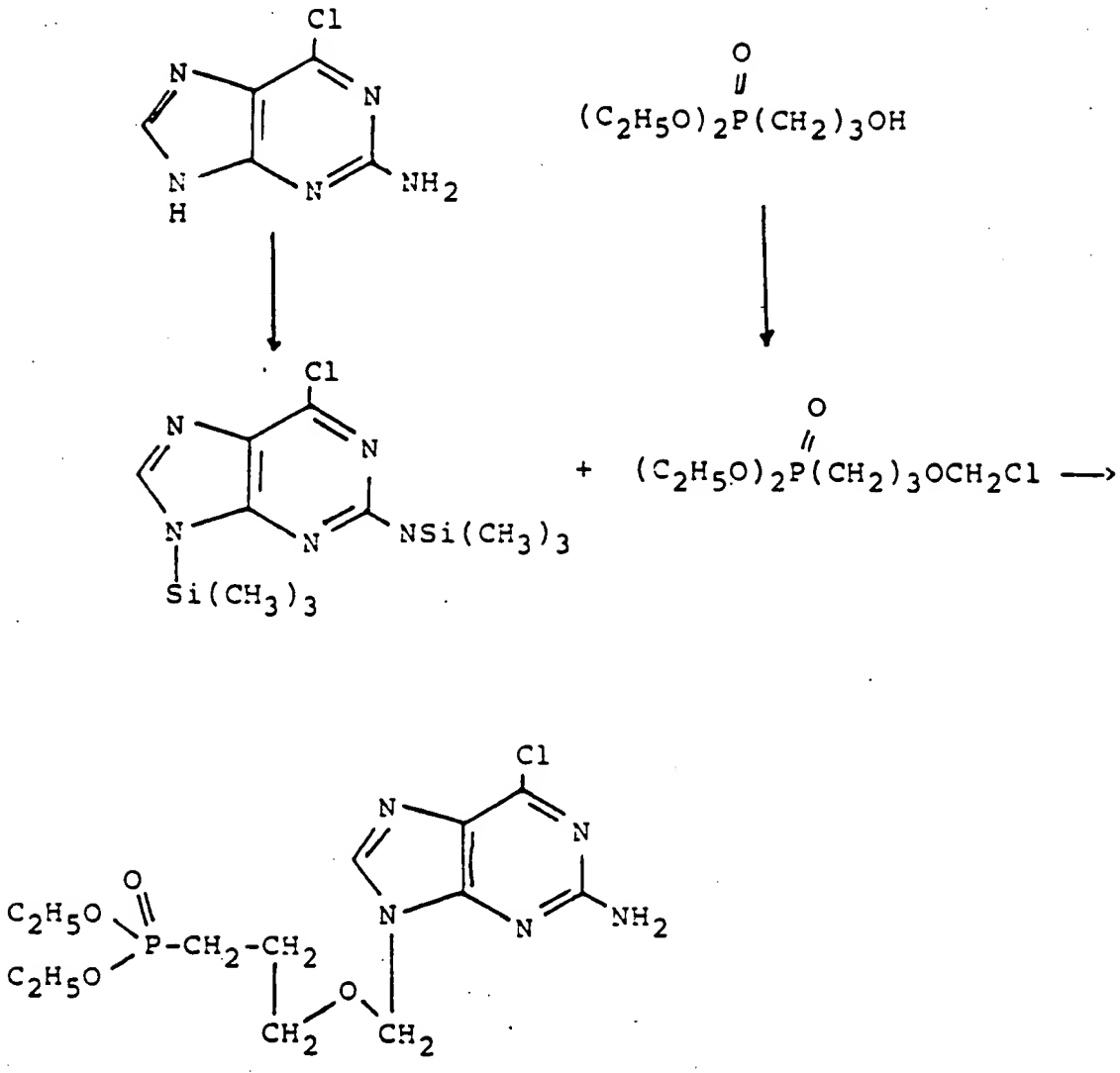
To 9.40 mmol silated guanine (James L. Kelley, Mark P. Krochmal, and Howard J. Shaeffer, J Med Chem, 24 1528-1531 (1981)) in 9 ml dry toluene was added 7.60 mmol diethyl-3-chloromethoxypropylphosphonate, prepared from diethyl-3-hydroxypropylphosphonate according to the procedure of Kelley, et al, followed by the addition of 2.2 ml triethylamine. The reaction was refluxed 24 hours and evaporated to dryness in vacuo. The residue was digested with 70 ml EtOH and the voluminous tan solid was isolated by suc-

BUREAU OMPI WIPO

tion filtration. The solid was dissolved in water, made basic with conc. NH_4OH, and treated with excess aqueous lead diacetate. The lead salt was isolated by centrifugation and dissolved in 50% acetic acid followed by treatment with H_2S for 20 minutes. The black lead sulfide was removed by suction filtration through Celite. The filtrate was evaporated to dryness in vacuo, triturated in EtOH, and filtered. The residue was further triturated in DMF and filtered to yield 320 mg off-white solid. This solid was dissolved in minimum water, acidified with 1 M HCl. Thereafter it was neutralized with 1 M NaOH and lyophilized. The solid residue was triturated in a mixture of DMF, H_2O, and EtOH and filtered to yield 276 mg of 9(3-phosphono-1-propyloxymethyl) quanine as a white solid (8.3%). Anal. ($C_9H_{12}N_5O_5P \cdot 2Na \cdot 5H_2O$) C, H, N; UV γ_{max} (ε): pH 1, 255 (14, 700); pH 7, 251 (15, 600); pH 11, 257 (12, 800), 267 (12, 800); mass spectrum (TMS derivative) m/e 591 (M^+ of TMS_4 derivative); ^1H NMR (D_2O): δ 1.25-1.90 (m, 4 H), 3.42 (tr, 2 H), 5.50 (s, 2 H), 7.92 δ (s, 1 H). Thin layer chromatography on SiGF developed with 7:3 CH_3CN:0.1 N NH_4Cl gave R_f 0.20.

BUREAU OMPI WIPO INTERNATIONAL

Example II



6-Chloro-9(3-diethylphosphono-1-propyloxy-methyl)guanine

To 0.5 g (2.95 mmol) 2-amino-6-chloropurine, silated and treated with $Hg(CN)_2$ according to the procedure of Robins and Hatfield (Morris J. Robins and Peter W. Hatfield, Can J Chem, 60 547-553 (1982)) in 40 ml benzene was added a solution of 2.68 mmol

BUREAU OMPI WIPO

diethyl-3-chloromethoxypropylphosphonate prepared from (0.525 g) diethyl-3-hydroxypropylphosphonate according to the procedure of Kelley, et al, (James L. Kelley, Mark P. Krochmal and Howard J. Shaeffer, J Med Chem, 24 1528-1531 (1981)). The reaction was refluxed for 2 hours, cooled and 400 ml $CHCl_3$ was added. The organic phase was washed successively with 80 ml each of aqueous saturated $NaHCO_3$ and 1 M aqueous KI. The organic solution was dried over Na_2SO_4, filtered and evaporated to 790 mg of yellow gum. A portion of this crude material was used to conduct hydrolysis experiments. The remaining material was chromatographed on a silica column. A solution of 574 mg of the crude reaction product was placed on 20 g silica packed in a column using 5:3 EtOAc:nPrOH. Elution with the same mixed solvent afforded sixteen fractions of 10-20 ml each. Fractions 7-12 were combined to yield 258 mg of a colorless oil which spontaneously crystallized. Trituration in $CH_2Cl_2 \cdot Et_2O$ afforded two crops of white solid (207 mg), mp 109-110° (28%). A yield of 46% was obtained from a reaction performed on 45.2 mmol of the starting purine. Anal ($C_{13}H_{21}ClN_5O_4P$) C_1H_1N; UV γ_{max} (ε): pH 1, 246 (ε 6600), 310 (7200); pH 7, 247 (6800), 308 (7400); pH 11 247 (6600), 308 (7100); mass spectrum: m/e 377 (M^+); ^1H NMR ($CDCl_3$): δ 1.3 (tr, 6 H), 1.52-2.18 (m, 4 H), 3.58 (tr, 2 H), 4.09 (qu, 4 H), 5.48 (s. with broad base, 4 H), 7.89 (s, 1 H). Thin layer chromatography on SiGF developed with 5:3 EtOAc:nPrOH gave R_f 0.40.

9(3-ethylphosphono-1-propyloxymethyl)guanine

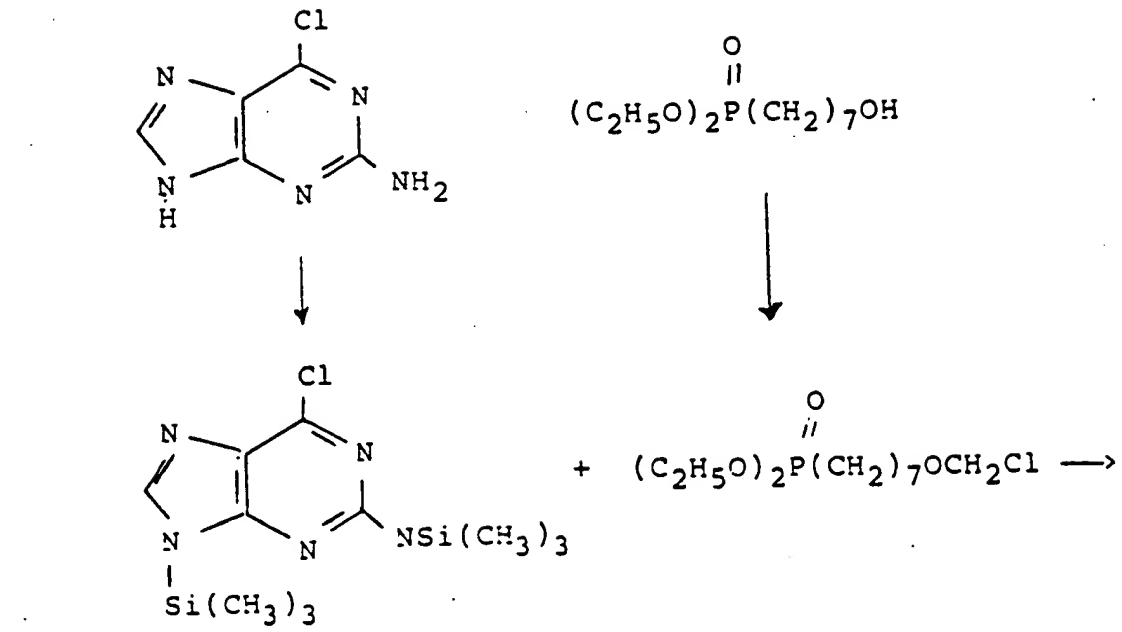
6-Chloro-9(3-diethylphosphono-1-propyloxymethyl)guanine (75 mg; 0.2 mmol) was combined with 5 ml 1 N aqueous NaOH and refluxed 1 hour. The cooled

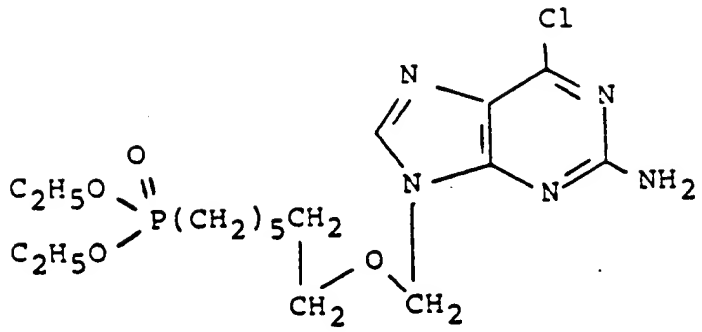
BUREAU OMPI WIPO INTERNATIONAL

reaction was neutralized with Dowex 50X8 (pyridinium form) and filtered, rinsing liberally with water. The solution was partially evaporated to remove pyridine and was then lyophilized. The orange-colored residue (74 mg) was redissolved in H_2O and centrifuged to remove insoluble material. The decanted solution (2 ml) was chromatographed on a 0.9 x 46 cm column of Whatman DE-52 Cellulose, HCO_3 form, using a linear gradient of one liter each H_2O and 0.2 M NH_4HCO_3 after an initial H_2O elution. Fractions (7 ml each) 43-47 yielded 25 mg (36%) of fluffy white solid after three lyophilizations. Electron impact mass spectrum (TMS derivative) showed m/1 547 (M^+ of TMS derivative); chemical ionization mass spectrum (TMS derivative) showed m/1 548 (M^+ + H of TMS_3 derivative). ^1H NMR (D_2O) showed δ 1.19 (tr, 3 H), 1.4-1.9 (m, 4H), 3.59 (tr, 2 H), 3.90 (quintet, 2 H), 5.47 (s, 2 H), 8.2 (br·s, 1 H). Thin layer chromatography behavior on SiGF: Rf 0.40 when developed with 7:3 CH_3CH. 0.1 N aqueous NH_4Cl. The material had a formula of ($C_{11}H_{18}N_5O_5P \cdot H_2O$) Calc: C-37.82% H-5.77%, N-20.0. Found: C-38.27%, H-5.84%, N-19.65%. A UV spectum was run on the material and showed UV γ_{max} (ε): pH 1, 256 (10, 400), 278 shoulder; pH 7, 252 (11, 300) 271 shoulder; pH 11, 256-258 (9, 600) 267 shoulder. The product was relyophilized.

BUREAU OMPI INT WIPO

Example III



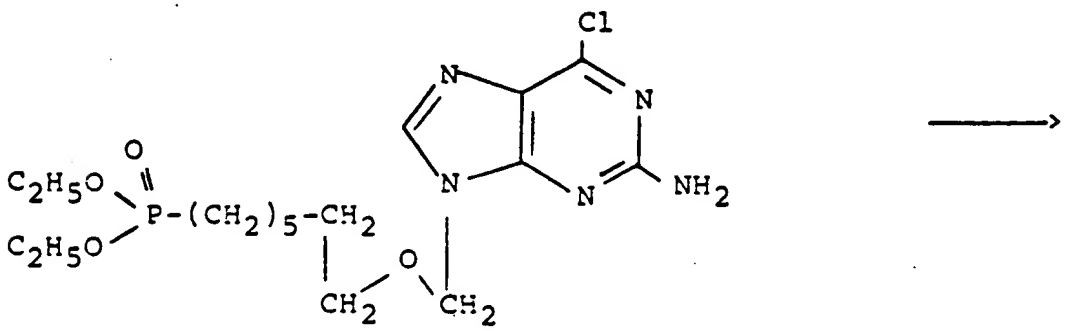


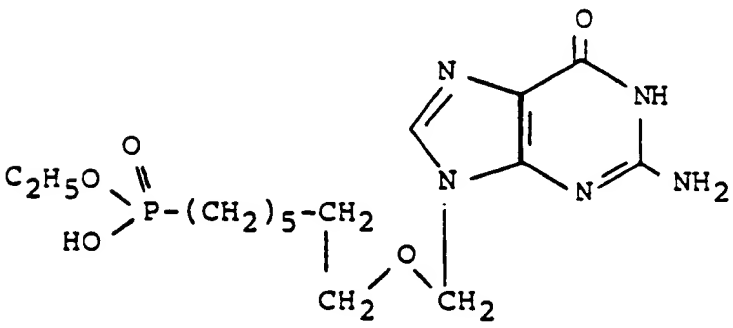
6-Chloro-9(7-diethylphosphono-1-heptyl-methyl)guanine

Diethyl 7-chloromethoxyheptylphosphonate was prepared from 1,7-dibromoheptane and triethylphosphite by the procedures used to prepare diethyl 3-chloromethoxypropylphosphonate (Example I). It was reacted with silated 2-amino-6-chloropurine, and mercuric cyanide as described for the preparation of 6-chloro-9(3-diethylphosphono-1-propyloxymethyl)guanine (Example II) to give 32% of product as

BUREAU OMPI WIPO

a colorless gum. UV γ_{max} pH 1: 246 nm (ε 6220), 310 nm (ε 6380); γ_{max} pH 7, 247 nm (ε 5910), 310 nm (ε 6410); γ_{max} pH 11, 246 nm (ε 5950), 309 nm (ε 6380); mass spectrum ^{1}H NMR ($CDCl_3$) ∫ 1.1-1.9 (m, 18 H), 3.48 (t, 2 H), 4.10 (q, 4 H), 5.47 (s, 2 H), 5.88 (s, 2 H), 7.93 (s, 1 H). Thin layer chromatography on silica gel GF gave R_f 0.15 using ethylacetate:ethanol (100:1).





<u>9-(7-ethylphosphono-1-heptyloxymethyl)guanine:</u> 6-chloro-9(7-diethylphosphono-1-heptyloxy-methyl)guanine was hydrolyzed by refluxing 1 N aqueous sodium hydroxide for 4 hours and isolated in 30% yield as described for the preparation of 9-(3-ethylphosphono-1-propyloxymethyl)guanine (Example II). It had R_f 0.5 on silica gel GF using acetonitrile (7:3) 0.1 N aqueous ammonium chloride. Proton NMR (D_2O) 1.1-1.5 (m, 15 H), 3.5 (t, 2 H), 3.90 (q, 2 H), 5.45 (s, 2 H) UV.

BUREAU OMPI WIPO

Biological Testing

The compounds of Example I and II were evaluated in vitro as antiviral agents against herpes virus.

The virus strain employed was Strain McCrae of type 1 herpes (thymidine kinase positive virus) prepared and titered in MA-104 cells and frozen at -90°C until use.

Continuous passaged monkey kidney (MA-104) cells were used, with growth medium consisting of Minimum Essential Medium (MEM) supplemented with 0.1% $NaHCO_3$ and 9% fetal calf serum. Test medium consisted of MEM supplemented with 2% fetal bovine serum, 0.18% $NaHCO_3$ and 50 µl gentamicin.

The last compounds were added to test medium at a concentration of 2000 µg/ml for use as a positive control.

Antiviral Test Method

To a 96 well microtiter plate containing an established 24 hour monolayer of cells from which the medium has been decanted was added 0.1 ml of varying (one-half log_{10}) concentrations of test compound, which incubated on the cell 15 minutes, after which 0.1 ml of virus in a concentration of 320 cell culture 50% infectious doses (CCID50)/0.1 ml was added. The plate was covered with plastic wrap and incubated at 37°C. Included with the test were toxicity controls (each concentration of compound + test medium in place of virus), virus controls (virus + test medium in place of compound) and cell controls (test medium in place of compound and virus). The cells were examined microscopically after 72 hours for evidence of cytotoxicity and for viral cytopathic effect (CPE). Vidarabine was run on the same plate in parallel.

BUREAU OMPI WIPO INTERNATIONAL

Antiviral activity was determined by observation of inhibition of viral CPE. This activity was expressed by minimum inhibitory concentration (MIC), defined as that dose range of compound causing 50% CPE inhibition. A Virus Rating (VR) was also determined, which is a numerical expression of antiviral activity, weighted to take into account any cytotoxicity observed. Generally, a VR of 0.1 - 0.4 is usually indicative of slight antiviral effect, 0.5 - 0.9 indicates moderate antiviral effedt, and $\geq$1.0 implies strong antiviral activity.

The results of these are summarized in tables A and B. The test compound had a strong activity against the thymidine kinase positive type I herpes virus. The activity was considered equivalent to that of vidarabine.

BUREAU OMPI WIPO INTERNATIONAL

TABLE A

Effect of compound of Example I and Vidarabine on Thymidine Kinase-Positive Type 1 Herpes Virus Infections in MA-104 Cells

Compound of I		Vidarabine	
Conc. (μg/ml	CPE[a] Inhib. (%)	Conc. (μ/ml)	CPE[a] Inhib. (%)
1000	100	1000	100
320	94	320	100
100	79	100	87
32	62	32	87
10	49	10	69
3.2	28	3.2	28
1.0	31	1.0	56
0		0	
VR[b]	1.4	1.3	
MIC[c]	10	10	

[a]Cytopathic effect, % cell alteration or destruction.

[b]Virus rating, a numerical expression of antiviral activity (Sidwell et al, Appl Microbiol, 22:797, (1971), 0.1 - 0.4 = slight activity, 0.5 - 0.9 = moderate activity, $\geq$ 1.0 = strong activity.

[c]Minimum inhibitory concentration - that dosage range wherein a 50% CPE inhibition is seen.

BUREAU OMPI WIPO INTERNATION

TABLE B

Effect of compound of Example II and Vidarabine on Thymidine Kinase Positive Type 1 Herpes Virus in MA-104 Cells (Two Tests)

Compound of II			Vidarabine (Control)		
Conc. (µg/ml	Test1 CPE[a] Inhib. (%)	Test2 CPE[a] Inhib. %	Conc. (µ/ml)	Test1 CPE[a] Inhib. (%)	Test2 CPE[a] Inhib. (%)
1000	100	76	1000	100	100
320	82	67	320	100	100
100	47	57	100	96	85
32	6	57	32	96	57
10	38	48	10	60	39
3.2	96	52	3.2	2	0
1.2	69	48	1.0	0	0
0			0		
VR[b]	>2.0	>1.4	VR[b]	0.8	07
MIC[c]	<1.0	<1.0	MIC[c]	10	10
MTD[d]	320	>1000		10	10

[a]Cytopathic effect, % cell alteration or destruction.

[b]Virus rating, a numerical expression of antiviral activity (Sidwell et al, Appl Microbiol 22:797, (1971), 0.1 - 0.4 = slight activity, 0.5 - 0.9 = moderate activity, ≥ 1.0 = strong activity.

[c]Minimum inhibitory concentration - that dosage range wherein a 50% CPE inhibition is seen, µg/ml.

[d]Maximum tolerated dose, µg/ml.

BUREAU OMPI WIPO INTERNATIONAL

The compound of Example II was further evaluated by the above-described *in vitro* test method against cytomegalo virus. The compound was strongly active with a VR of 2.1-2.3.

The compound of Example II was tested *in vivo* in guinea pigs as an agent against thymidine kinase positive herpes virus. The animals were innoculated with the virus. Eighteen hours later the material of Example II (0.4% solution in water or 1-2% solution), a 5% solution of acyclovir or a 1.4% solution of poly(vinylalcohol) was administered and five days later blister diameters at the point of innoculation were measured. Satellite lesions were measured as well.

The results of these tests are given in Table C and show that the compound has superior activity against TK^+ virus.

TABLE C

Effect of Compound of Example II *in vivo* against Herpes Virus

Virus	Placebo, 1.4% poly(vinylalcohol)	Acyclovir, 5%	Cx of II 1-2%*	Cx of II 0.4%
TK^+	1.7**	1.0	0.9	2.1
Satellite lesions	9	4	6	11

*saturated solution

**average number of lesions

BUREAU OMPI WIPO INTERNATIO

Formulations

The following formulations based on the compounds of the invention and their preparation are representative.

A formulation suitable for injections intramuscularly or intraperitoneally is prepared by combining the first four of the following materials

Compound of the Invention	1 gram
Poly(ethylene glycol)	50 grams
Propylene glycol	50 grams
Tween 80 suspension agent	1.5 grams
Injectable Saline	200 ml

and then adding the last material. The material forms a clear solution which is filtered and sealed in sterile containers.

A simple intravenous injection formulation is formed by dissolving 1 gram of an active compound in 250 ml of injectable saline which after filtering is packaged in sterile bottles.

A cream for topical administration is formulated by stirring 10 g of active compound of the invention with 20 g of mineral oil, 40 g of petroleum jelly, 0.3 g of mixed methyl/propyl paraben and 5 g of nonionic surfactant at 50°C. Then 150 ml of water are stirred into the mixture at 50°C at high speed to form a cream and the mixture is cooled and packaged in capped tubes.

An oral dosage form is prepared from 10 g of compound of the invention, 100 g of lactose, and 1 g of starch which are mixed with 0.1 g of magnesium stearate in methanol to granulate. The methanol is removed by gentle heating with stirring. A portion of this material is retained as a granular powder for oral use while the remainder is hand formed into 250 mg tablets in a manual tableting machine.

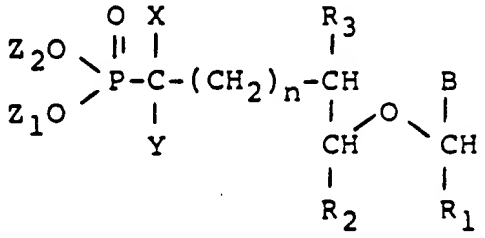
BUREAU OMPI WIPO INTERNATIONAL

The foregoing examples and formulations have been presented to illustrate the present invention and are not to be construed as limitations on the invention's scope which is instead defined by the following claims.

BUREAU OMPI WIPO INTERNATIONAL

What is Claimed is

1. A compound having the structure



wherein Z_1 and Z_2 are the same or different and selected from the group made up of hydrogen, the one to six carbon alkyls, phenyl and benzyl, X is H, OH, or together with Y = O, Y is H or together with X = O, n is an integer, 0, 2 or 4, R_1 and R_2 together complete a β-pentofuranose sugar or R_1 is H and R_2 is H or $-CH_2OH$, R_3 is H or OH and B is a purine or pyrimidine base.

2. The compound of claim 1 wherein R_1 and R_2 together complete a β-pentofuranose sugar.

3. The compound of claim 2 wherein B is selected from guanine, adenine, 5-iodouracil, 5-trifluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil, 5-propyluracil and 5-ethyluracil.

4. The compound of claim 2 wherein n is 0.

5. The compound of claim 2 wherein n is 2.

6. The compound of claim 2 wherein n is 4.

7. The compound of claim 2 wherein the β-pentofuranose is a β-ribofuranose.

BUREAU OMPI WIPO INTERNATIONAL

8. The compound of claim 2 wherein the β-pentofuranose is a β-arabinofuranose.

9. The compound of claim 2 wherein Z_1 and Z_2 are each selected from the group made up from hydrogens and one to four carbon alkyls.

10. The compound of claim 9 wherein n is 0.

11. The compound of claim 9 wherein n is 2.

12. The compound of claim 9 wherein n is 4.

13. The compound of claim 2 wherein X and Y are each hydrogens.

14. The compound of claim 2 wherein X and Y together are =0.

15. The compound of claim 2 wherein X is hydroxyl and Y is hydrogen.

16. The compound of claim 1 wherein R_1 is hydrogen and R_2 is hydrogen.

17. The compound of claim 16 wherein B is selected from guanine, adenine, 5-iodouracil, 5-trifluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil, 5-propyluracil and 5-ethyluracil.

18. The compound of claim 16 wherein Z_1 and Z_2 are each selected from the group made up of hydrogen and one to four carbon alkyls.

BUREAU OMPI WIPO INTERNATIONAL

19. The compound of claim 18 wherein X and Y are each hydrogens.

20. The compound of claim 18 wherein X and Y together are =0.

21. The compound of claim 18 wherein X is hydroxyl and Y is hydrogen.

22. The compound of claim 19 wherein n is 0.

23. The compound of claim 19 wherein n is 2.

24. The compound of claim 19 wherein n is 4.

25. The compound of claim 1 wherein R_1 is hydrogen and R_2 is hydroxymethyl.

26. The compound of claim 25 wherein B is selected from guanine, adenine, 5-iodouracil, 5-trifluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil, 5-propyluracil and 5-ethyluracil.

27. The compound of claim 25 wherein Z_1 and Z_2 are each selected from the group made up of hydrogen and one to four carbon alkyls.

28. The compound of claim 27 wherein X and Y are each hydrogens.

29. The compound of claim 27 wherein X and Y are =0.

BUREAU OMPI WIPO INTERNATIONAL

30. The compound of claim 27 wherein X is hydroxyl and Y is hydrogen.

31. The compound of claim 28 wherein n is 0.

32. The compound of claim 28 wherein n is 2.

33. The compound of claim 28 wherein n is 4.

34. A metal salt of a compound of claim 1.

35. A pharmaceutical preparation comprising a compound of claim 1 in a pharmaceutically acceptable carrier.

36. A method for treating herpes in a mammal in need of such treatment comprising administering to said mammal an effective herpes-treating dose of the preparation of claim 35.

BUREAU OMPI WIPO INTERNATIONAL

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 84/00737

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3]: C 07 H 19/10; C 07 H 19/20; C 07 F 9/65; A 61 K 31/00; A 61 K 31/675

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[3]	C 07 H 19/00; C 07 F 9/00; A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X,Y	GB, A, 1243213 (SYNTHEX) 18 August 1971 see pages 9-11; pages 20-22 --	1-34
X,Y	DE, A, 2009834 (SYNTHEX) 17 September 1970 see pages 64-73 --	1-34
X,Y	FR, A, 2381781 (WELLCOME) 22 September 1978 see pages 1-5 --	1-36
X,Y	DE, A, 3045375 (ROBUGEN) 1 July 1982 see pages 1-5 --	1-36
X,Y	EP, A, 0074306 (MERCK & CO.) 16 March 1983 see pages 1-11 --	1-36
X,Y	EP, A, 0049072 (EMS BIOLOGICALS) 7 April 1982 see pages 1-13 --	1-36 ./.

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
24th October 1984	26 NOV. 1984
International Searching Authority [1]	Signature of Authorized Officer [20]
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (October 1981)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with Indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
X,Y	US, A, 3560478 (T. MEYERS) 2 February 1971 see claims 1-6	1-34
X,Y	US, A, 3446793 (C. JONES) 27 May 1969 see claims 1-3	1-34
X,Y	Journal of Medicinal Chemistry, vol. 22, no. 1, January 1979 J.A. Montgomery et al.: "Phosphonate analogue of 2'-Deoxy-5-fluorouridylic acid", pages 109-111, see pages 109-110	1-36
X,Y	Journal of Heterocyclic Chemistry, vol. XI, February, April, June 1974 J.A. Montgomery et al.: "The use of the wittig reaction in the modification of purine nucleosides (1)", pages 211-218, see page 213	1-34
X,Y	Journal of the American Chemical Society, vol. 92, no. 18, 9 September 1970 G.H. Jones: "Communications to the editor. Synthesis of Isosteric Phosphonate analogs of some biologically important phosphodiesters", pages 5510-5511, see pages 5510-5511	1-34
X,Y	Journal of the American Chemical Society, vol. 90, no. 19, 11 September 1968 G.H. Jones et al.: "The Synthesis of 6'-Deoxyhomonucleoside-6'-phosphonic Acids", pages 5337-5338, see pages 5337-5338	1-34
X,Y	Liebigs Annalen der Chemie, vol. 1, 1984, Verlag Chemie (Weinheim, DE) J. Hollmann et al.: "Darstellung und Konformationszuordnung einiger 5'-homologer Adenosinderivate", pages 98-107, see page 99	1-34
X,Y	Chemical Review, no. 3, June 1977 R. Engel: "Phosphonates as analogues of natural phosphates", pages 349-367, see page 351	1-34
X,Y	Biochemistry, vol. 12, no. 9, 24 April 1973; A. Hampton et al.: "Synthesis of homoadenosine-6'-phosphonic acid and studies of its substrate and	./.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
	inhibitor properties with adenosine monophosphate utilizing enzymes", pages 1730-1736, see page 1732	1-36

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ....., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

- claims 1-8,34-36
- claims 1-8,34-36
- claims 9-36
- claims 9-36

For explanation: see Form PCT/ISA/210 supplemental sheet 3

1. ☒ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM Form PCT/ISA/210 - supplementel sheet 2

- 1-8,34-36 : Compounds of the formula on page 40 with R1 and R2 completing a pentofuranose ring and B being a purine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations
- 1-8,34-36 : Compounds of the formula on page 40 with R1 and R2 completing a pentofuranose ring and B being a pyrimidine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations
- 9-36 : Compounds of the formula on page 40 with R1:H and R_2H or CH_2OH and B being a purine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations
- 9-36 : Compounds of the formula on page 40 with R1:H and R_2H or CH_2OH and B being a pyrimidine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations

---

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/11/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A- 1243213	18/08/71	GB-A-	1243214	18/08/71
		DE-A-	1768944	05/01/72
		CH-A-	537392	13/07/73
		US-A-	3662031	09/05/72
		US-A-	3878194	15/04/75
DE-A- 2009834	17/09/70	FR-A-	2034785	18/12/70
		GB-A-	1301182	29/12/72
FR-A- 2381781	22/09/78	NL-A-	7802111	28/08/78
		BE-A-	864316	24/08/78
		DE-A-	2808096	31/08/78
		LU-A-	79126	17/10/78
		JP-A-	53108999	22/09/78
		AT-B-	353286	12/11/79
		AU-A-	3356078	30/08/79
		CA-A-	1094062	20/01/81
		GB-A-	1590500	03/06/81
		US-A-	4287188	01/09/81
		AU-B-	521577	22/04/82
		SE-A-	7802140	25/08/78
		SE-B-	430507	21/11/83
		CH-A-	643858	29/06/84
		AT-B-	366055	10/03/82
DE-A- 3045375	01/07/82	None		
EP-A- 0074306	16/03/83	AU-A-	8755282	03/03/83
		JP-A-	58077881	11/05/83
EP-A- 0049072	07/04/82	JP-A-	57085373	28/05/82
		AU-A-	7527381	25/03/82
		US-A-	4347360	31/08/82
US-A- 3560478	02/02/71	None		
US-A- 3446793	27/05/69	None		